CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-629

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-629	Submission Date(s): 06/18/03
Brand Name	Apidra™
Generic Name	Insulin glulisine (rDNA origin) injection
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Metabolic and Endocrine Drug Products (HFD-510)
Sponsor	Aventis
Relevant IND(s)	IND 61,956
Submission Type; Code	NME, S1
Formulation; Strength(s)	Solution, 100 IU/ml (10 ml/vial)
Dosing regimen	The dosage should be individualized based on hyperglycemia and should normally be used in regimens that include a longer-acting insulin or basal insulin analog.
Indication	Type 1 or insulin-dependent diabetes mellitus (IDDM) Type 2 or non-insulin-dependent diabetes mellitus (INDDM)

1 Executive Summary

On June 18, 2003, Aventis submitted NDA 21-629 for insulin glulisine (Apidra™) 100 IU/ml for injection. Insulin glulisine is a rapid acting insulin analog produced by recombinant DNA utilizing a non-pathogenic laboratory strain of *Escherichia coli*. Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. Insulin glulisine is designed to provide diabetic patients with insulin at a meal time to control postprandial hyperglycemia. Dosing is dependent on individual patient's glucose levels. The sponsor provided 14 human studies to support "Human Pharmacokinetics and Biopharmaceutics", of which 3 studies were performed using initial stage formulations during the early drug development. Most studies were conducted in South Africa using the euglycemic clamp technique.

The absolute bioavailability of insulin glulisine after femoral, deltoid and abdominal subcutaneous injections of 0.1 IU/kg and an i.v. injection of 0.1 μIU/kg were 68%, 71% and 73%, respectively. Compared to the abdominal injection, the relative bioavailability of glulisine was 93% after femoral and 98% after deltoid injections, respectively.

Dose proportionality was assessed with two doses, 0.1 IU/kg and 0.3 IU/kg. Cmax was proportional. The total exposure after 0.1 IU/kg was slightly under-proportional to 0.3 IU/kg while the early exposure ($AUC_{0\text{-}2h}$) was close to proportional. The pharmacodynamic response of 0.3 IU/kg insulin glulisine exceeded that of 0.1 IU/kg, but it was not proportional.

Distribution and elimination of insulin glulisine and regular human insulin were assessed in healthy subjects after continuous intravenous infusion over 2 hours of 0.8 mIU/kg/min insulin glulisine and

regular human insulin. The volume of distribution is 13L and 21L for insulin glulisine and regular human insulin, respectively. The elimination half-life is 13 min and 17 min for insulin glulisine and human insulin, respectively. The clearance is 912 mL/min and 1102 mL/min, respectively.

Insulin glulisine injected immediately before a meal provides similar overall glucose disposal in type 1 diabetic subjects compared to regular human insulin injected 30 min before a meal. Insulin glulisine provides more rapid onset of action and shorter time to maximum glucose excursion compared to regular human insulin.

Time to peak concentrations (Tmax) for insulin glulisine is 51 min compared to 58 min and 82 min for insulin lispro and regular human insulin, respectively. All pharmacokinetics and pharmacodynamic studies have demonstrated that insulin glulisine exhibits rapid action and shorter duration of action compared to regular human insulin.

The pharmacodynamic assessment has demonstrated that insulin glulisine is equipotent on a molar basis to regular human insulin by comparing the steady state pharmacodynamics during a continuous intravenous infusion of 2 h of 0.8 mIU/kg/min of glulisine or regular insulin using the euglycemic clamp technique.

The subjects with moderate and severe renal impairment showed the increased exposure of insulin glulisine by 22% to 40% in comparison with normal subjects and the clearance of insulin glulisine was reduced by 20 –25% in these subjects as well. There were statistically significant correlations for AUC(0-end) and CLtot/F between renal functions as measured by creatinine clearance though the degree of impact of moderate and severe renal impairment on insulin glulisine pharmacokinetic parameters remains similar. Regular human insulin has similar properties in renally impaired patients.

The pharmacokinetic profiles and time action of insulin glulisine of syringe-mixed versus simultaneously injected 0.1 IU/kg insulin glulisine and 0.2 IU/kg NPH insulin were studied. Premixed regimen attenuated the rapid acting properties of insulin glulisine since the peak exposure (Cmax) was decreased by 27% and the time to peak exposure (Tmax) was delayed by 3 min. The total glucose disposal [AUC(0-clamp end)] and maximum activity [GIRmax] were not affected. However, the time to peak glucose infusion rate was delayed by 34 min.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the original NDA21-629 for insulin glulisine to support the section of human pharmacokinetics and biopharmaceutics. OCPB has found that the clinical pharmacology information is acceptable from a standpoint of clinical pharmacology and biopharmaceutics. This recommendation, labeling recommendation and comments should be sent to the sponsor as appropriate.

1.2 Phase IV Commitments

None.

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3 Summary of CPB Findings

Pharmacokinetics

- **Absolute and relative bioavailability:**

The absolute bioavailability of glulisine after femoral, deltoid and abdominal subcutaneous injections of 0.1 IU/kg and an i.v. bolus of 0.1 IU/kg were 68%, 71% and 73%, respectively. Compared to the abdominal injection, the relative bioavailability of glulisine was 93% for femoral and 98% for deltoid injections.

- **Time to peak concentrations:**

Through the drug development program, all pharmacokinetic s and pharmacodynamic studies have demonstrated that insulin glulisine exhibits a rapid action and shorter duration of action compared to human regular insulin. Its properties are very similar to insulin lispro, but it appears to act a little more rapid than insulin lispro.

Table 1. Comparison of Tmax of insulin glulisine, insulin lispro and human regular insulin in different populations

Study	Population	Dose (s.c.)	Tmax (min)			Mean residence time (MRT) (min)		
			Glulisine	Lispro	Regular insulin	Glulisine	Lispro	Regular insulin
1005	Type 1 Diabetes	0.2 IU/kg	51	58	82	96	131	185
1006	Type 2 Diabetes	0.2 IU/kg	85	73	93	144	198	262
1009	Healthy subjects	0.3 IU/kg	56	50	99	105	117	182
1010	Obese healthy subjects	0.2 IU/kg	76	99	144	149	166	229

- **Meal time:**

Insulin glulisine injected immediately before a meal provides similar overall glucose disposal in type 1 diabetic subjects compared to regular human insulin injected 30 min before a meal. Insulin glulisine provides more rapid onset of action and shorter time to maximum glucose excursion.

- **Dose proportionality:**

Dose proportionality was assessed in Study 1009, in which two doses, 0.1 IU/kg and 0.3 IU/kg were used. Cmax was proportional. The total exposure after 0.1 IU/kg was slightly under-proportional to 0.3 IU/kg while the early exposure (AUC0-2h) was close to proportional (Table 2). However, the pharmacodynamic response of 0.3 IU/kg insulin glulisine exceeded that of 0.1 IU/kg, but dose proportionality was not observed.

Table 2. Dose proportionality of pharmacokinetics of insulin glulisine after dose normalization

Parameter	Geometric mean (N=16)		Point estimate (95% CI)
	0.1 IU/kg	0.3 IU/kg	0.1 IU/kg / 0.3 IU/kg
Cmax [μIU/mL]	193	196	98% (83; 116)
AUC (0-2h) [μIU.min/mL]	16824	18004	93% (78; 112)
AUC(0-clamp end) [μIU.min/mL]	22396	29302	76% (66; 89)

- **Protein binding:**

Studies were not conducted.

- **Metabolism:**

Studies were not conducted.

- **Distribution /Elimination**

In Study 1016, the distribution and elimination of insulin glulisine and regular human insulin were assessed in healthy subjects after continuous intravenous infusion over 2 hours of 0.8 mIU/kg/min glulisine and human insulin. The distribution and elimination of glulisine and human insulin were similar and reflect a fast elimination from the systemic circulation after IV administration (Table 3).

Table 3. Distribution and elimination of insulin glulisine and RHI

Parameter	Geometric mean (N=16)	
	Glulisine	Human insulin
Volume of distribution (L)	13	21
Elimination half-life (min)	13	17
Total clearance (mL/min)	912	1102

- **Special populations:**

Renal

The subjects with moderate and severe renal impairment showed the increased exposure of insulin glulisine by 22% to 40% in comparison with normal subjects and the clearance of insulin glulisine was reduced by 20 –25% in these subjects as well. There were statistically significant correlations for AUC(0-end) and CLtot/F between impaired renal functions and normal renal function as measured by creatinine clearance.

Race

The AUC ratios of the first hour to the total exposure for insulin glulisine were 33% in Japanese and 21% in Caucasians, respectively. The corresponding ratios for the pharmacodynamic response was 13% for Japanese and 11% for Caucasians, respectively. Similar findings were observed for lispro and human

regular insulin as well. Japanese subjects appear to have more rapid absorption rate for all insulin drug products than Caucasians.

- **Pharmacodynamics:**

The pharmacodynamic assessment has demonstrated that insulin glulisine is equipotent on a molar basis to human regular insulin by comparing the steady state pharmacodynamics during a continuous i.v. infusion of 2 h of 0.8 mIU/kg/min of glulisine or regular insulin using the euglycemic clamp technique.

Table 4. Steady state pharmacodynamics of 0.8 mIU/kg/min glulisine and RHI (Study 1016)

Variable	Sample mean (n = 16)		Point estimate (90% confidence interval) #
	Regular human insulin	Glulisine	Glulisine/ Regular human insulin
AUC_{SS} [mg/kg]	214.2	209.0	97.6% (88.4 ; 107.6%)
GIR_{SS} [mg/min·kg]	7.2	7.0	98.4% (89.3 ; 108.5%)
$AUC_{(0\text{-clamp end})}$ [mg/kg]	1049.7	994.8	94.8% (84.5 ; 106.2%)

- **Mixing insulin glulisine with human regular insulin:**

The pharmacokinetic profiles and time action of insulin glulisine of syringe-mixed versus Simultaneously injected 0.1 IU/kg insulin glulisine and 0.2 IU/kg NPH insulin were studied in 32 male healthy subjects using the euglycemic clamp technique. Premixed regimen showed that the peak exposure (Cmax) was decreased by 27% and the time to peak exposure (Tmax) was delayed by 3 min. The time to peak glucose infusion rate was delayed by 34 min. The total glucose disposal [AUC(0-clamp end)] and maximum activity [GIRmax] were not affected.

- **Analytical assay:**

Insulin glulisine was measured with a specific homologous radioimmunoassay (RIA), which uses the competition between glulisine and [redacted]. The LOQ was [redacted] with a working range of [redacted]. This assay does not cross-react with human insulin, pro-insulin or lispro and cross-reacts [redacted].

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Hydrochloric acid, concentrated [Hydrochloric acid] (a)	q. s. ad pH 7.3	acidifying agent
Water for injection	ad 1.00 mL	solvent

- **What is the proposed mechanism of drug action and the therapeutic indications?**

The primary activity of insulins and insulin analogs, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis in the adipocyte, inhibit proteolysis, and enhance protein synthesis.

The glucose lowering activities of APIDRA and of regular human insulin are equipotent when administered by the intravenous route. After subcutaneous administration, the effect of APIDRA is more rapid in onset and of shorter duration compared to regular human insulin.

- **What is the potency of insulin glulisine to lower blood glucose relative to human regular insulin?**

In Study 1016, biopotency was assessed by comparing the steady state pharmacodynamics during a continuous i.v. infusion of 2 h of 0.8 mIU/kg/min of glulisine or regular insulin, using the euglycemic clamp technique. Glulisine and regular insulin were equipotent on a molar basis (same dose) as attested by equivalent glucose disposal under steady state. These results support the ability of patients to interchange glulisine on a unit per unit basis with short acting insulins. Infusion of the same doses of glulisine and regular insulin produced equivalent glucose disposal at steady state as shown by equivalent GIR_{SS} and AUC_{SS} as well as AUC(0-clamp end) (Table 4).

4.2 GENERAL CLINICAL PHARMACOLOGY

- **What is absolute bioavailability of insulin glulisine? What is the effect of injection sites on the bioavailability of insulin glulisine?**

The absolute and relative bioavailability of glulisine were assessed in Study 1004 where healthy, male subjects received either a s.c. injection of 0.1 IU/kg in the femoral, deltoid, or abdominal area or an i.v. injection of 0.1 IU/kg. The absolute bioavailability of glulisine after femoral, deltoid and abdominal injections was 68%, 71% and 73%, respectively. The relative bioavailability of glulisine to the abdominal injection is 93% for femoral and 98% for deltoid injections, respectively, which demonstrates that there seems to be little effects of injection sites on the bioavailability of insulin glulisine.

Table 6. Absolute bioavailability

Parameter	Geometric mean (N = 16)			
	Intravenous administration.	Subcutaneous administration		
		Femoral	Deltoid	Abdominal
AUC (0-∞) [µIU.min/mL]	14862.5	10107.4	10596.9	10910.1
Cmax [µIU/mL]	3014.2	57	68.4	83.6
Tmax [min]	N/A	65.8**	57.8**	44.3**
Absolute bioavailability	N/A	68%	71%	73%

** Median values

- **What are the properties of insulin glulisine in pharmacokinetics and pharmacodynamics among patients with Type 1 and Type 2 Diabetes?**

Two clinical studies (1005 and 1006) were performed to compare the pharmacokinetics and pharmacodynamics of insulin glulisine to lispro and regular human insulin in type 1 diabetic patients (Study 1005) and in type 2 diabetic patients (Study 1006) after administration of 0.2 IU/kg insulin glulisine, insulin lispro and regular human insulin using the euglycemic clamp technique.

In type I diabetic patients, insulin glulisine presented a more rapid onset and a shorter duration of action than regular human insulin. The rapid acting properties of insulin glulisine were to some extent more pronounced than with insulin lispro in both pharmacokinetics and pharmacodynamics (Table 7).

In type 2 diabetic patients, insulin glulisine and insulin lispro presented with almost superimposable time action profiles, which displayed a more rapid onset of action and shorter duration of action after injection than regular human insulin with apparent equivalent efficacy in total glucose disposal. Insulin glulisine displays pharmacokinetic and pharmacodynamic properties in type 2 diabetic patients similar to insulin lispro (Table 7). Therefore, the study has demonstrated that insulin glulisine has rapid acting insulin properties like lispro in both types of diabetic patients.

Table 7. Comparison of PK and PD of insulin glulisine, lispro and human regular insulin in type 1 and type 2 diabetic patients.

Variable	Type 1 (N=16)			Type 2 (N=8)		
	Glulisine	Lispro	HRI	Glulisine	Lispro	HRI
Pharmacokinetics						
AUC (0-1h) [μIU.min/mL]	5005	3905	2198	2939	3183	1741
AUC(0-2h) [μIU.min/mL]	10625	8721	5412	7662	7622	4221
AUC(0-clamp end) [μIU.min/mL]	16120	16837	16610	18408	21093	19731
Cmax [μIU/mL]						
Tmax [min]	51	58	82	85	73	93
Pharmacodynamics						
AUC (0-1h) [mg/min/kg]	176	113	80	43	79	36
AUC (0-2h) [mg/min/kg]	625	556	348	218	350	136
AUC (0-clamp end) [mg/min/kg]	1547	1495	1473	1006	1305	1128
GIRmax [mg/kg/min]	8.2	8.3	5.9	5.5	7	5.5
Tmax [min]	98	94	161	167	165	266

Insulin glulisine has exhibited a little more rapid acting than Lispro in both exposure and response in type1diabetes. However, there is apparent difference for all the three insulin products between type 1 and type 2 diabetic patients. Type 2 diabetic patients have showed that slower time action profiles and less glucodynamic response assessed by the ratios of early exposure to total exposure (Table 8).

Table 8. Comparison of the ratios of early exposure/response to the total exposure/response in type 1 and type 2 diabetic patients.

Ratio	Type 1 (N=16)			Type 2 (N=8)		
	Glulisine	Lispro	HRI	Glulisine	Lispro	HRI
Pharmacokinetics						
AUC (0-1h)/ AUC(0-clamp end)	31.1%	23.2%	13.3%	16%	15%	8.9%
AUC (0-2h)/ AUC(0-clamp end)	66%	51.8%	32.6%	41.7%	36.2%	21.4%
Pharmacodynamics						
AUC (0-1h)/ AUC(0-clamp end)	11.4%	7.6%	5.5%	4.3%	6.1%	3.2%
AUC (0-2h)/ AUC(0-clamp end)	40.4%	37.2%	23.7%	21.7%	26.8%	12.1%

- **What are the properties in pharmacokinetics and pharmacodynamics of insulin glulisine injected subcutaneously before and after a standard meal in type 1 diabetic patients in comparison with human regular insulin?**

A single-dose (0.15 IU/kg), randomized, open, four-way crossover study in 20 type 1 diabetic patients was performed to compare the properties in the pharmacodynamic and pharmacokinetic parameters for insulin glulisine immediately before (within 2 min) a standard meal and 15 min after meal. Regular human insulin 30 min prior to a standardized meal and immediately before a standard meal (within 2 min) were also performed in the study. The study results are presented in the Figure 1 and summarized in Table 9.

Figure 1.

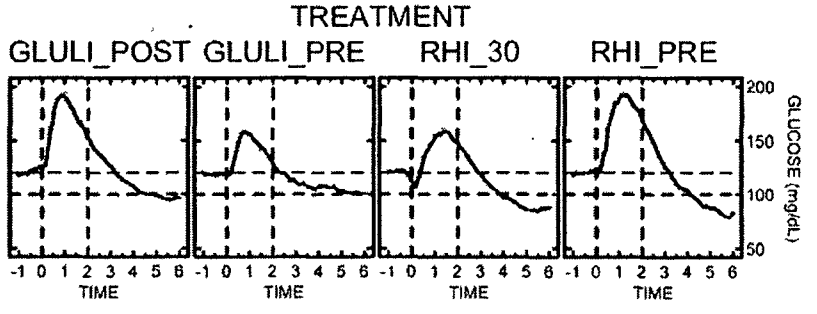


Table 9. Pharmacodynamic parameters of insulin glulisine injected before and after meal

Variable	Sample mean (n = 20*)			
	Glulisine (immediately before meal)	Glulisine (15 min after meal)	Regular insulin (30 min before meal)	Regular insulin (immediately before meal)
AUC (0-1h) [mg.h/dL]	137.7	172.7	113.2	151.0
AUC (0-2h) [mg.h/dL]	278.9	336.7	260.5	333.8
GLU max [mg/dL]	179.8	208.3	177.0	208.5
AUC (0-6h) [mg.h/dL]	707.7	776.5	715.4	770.4
tmax [min]	48.0	45.0	115.0	69.5
tmin [min]	275.0	254.5	325.0	310.5

Insulin glulisine injected immediately before a meal provides similar overall glucose disposal in type 1 diabetic patients compared to regular human insulin injected 30 min before a meal although regular insulin injected 30 min before meal exhibited a little better glucose control at the initial time represented by AUC (0-1h) and AUC (0-2h). And Insulin glulisine did provide more rapid onset of action and shorter time to maximum glucose excursion. Insulin glulisine injection 15 min after meal showed a similar profile of glucose control to regular human insulin injected immediately before meal though the first hour glucose control was better with regular human insulin. The sponsor claims that insulin glulisine can be injected either immediately before or after a meal to dispatch the postprandial glucose load.

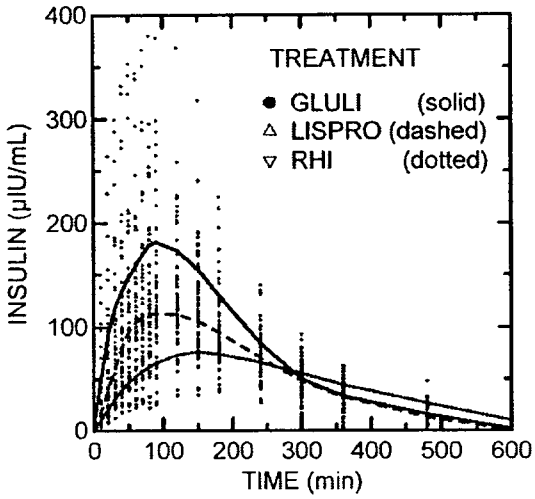
However, the data clearly shows that the postprandial blood glucose control by insulin glulisine administered immediately before the meal resembles that by regular human insulin injected 30 min before meal. Insulin glulisine administered 15 min after meal did not provide an optimal postprandial glucose control. Injection of insulin glulisine immediately before meal should be recommended as the time to be administered. As a measure when it is not possible to be administered or is missed immediately before a meal, insulin glulisine should be injected within 15 min after the start of a meal though the postprandial glucose control is not optimal.

- **What are pharmacokinetic and pharmacodynamic properties of insulin glulisine in comparison with lispro and regular insulin in obese subjects?**

A single-dose (0.3 IU/kg), randomized, double-blind, 3-way crossover study was performed to compare the pharmacokinetics and pharmacodynamics of insulin glulisine to regular human insulin and insulin lispro using the euglycemic clamp. 18 obese, healthy, non-diabetic subjects (30 – 40 kg/m) participated in the study with 9 subjects in each of the following two obesity classes (obesity class I: 30.0 – 34.9 kg/m 2; obesity class II: 35.0 – 40 kg/m 2).

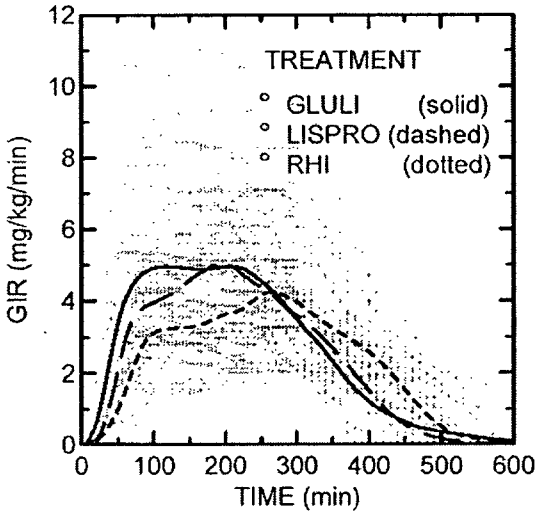
Insulin glulisine and insulin lispro both had more rapid and shorter residing pharmacokinetic profiles than regular human insulin as displayed by higher fractional AUCs, as well as Cmax, and shorter Tmax. The AUC(0-clamp end), which was similar for insulin lispro and regular human insulin, was larger after insulin glulisine, confounded by the use of different RIAs (Figure 2). Insulin glulisine had a slightly more rapid pharmacokinetic profile than insulin lispro, as displayed by slightly shorter Tmax and MRT by their median values. The study has demonstrated insulin glulisine maintains it's more rapid and shorter residing pharmacokinetic profile than human regular insulin in obese, non-diabetic subjects.

Figure 2. Average insulin concentrations (μIU/mL) after 0.3 IU/kg of insulin glulisine or insulin lispro or regular human insulin (RHI) injected subcutaneously in the abdominal area.



Insulin glulisine and insulin lispro both had more rapid acting profiles than regular human insulin. All fractional AUCs, as well as GIRmax, were greater for insulin glulisine and insulin lispro than for regular human insulin, though, similar AUC(0-clamp end) with all treatments indicating equivalent total glucose disposal. Insulin glulisine had a more rapid acting profile than insulin lispro as displayed by greater fractional AUCs (Figure 3).

Figure 3. Average glucose infusion rates (GIR, mg/min.kg) after 0.3 IU/kg of insulin glulisine or insulin lispro or regular human insulin injected subcutaneously in the abdominal area.



However, the weakness of this study is that it did not have subjects with normal weight as a control group for direct comparison. A cross-study comparison has to be made in order to compare the deference in pharmacokinetics/pharmacodynamics of insulin glulisine between obese and normal subjects.

- **What are the properties of insulin glulisine in pharmacokinetics and pharmacodynamics among healthy subjects and obese subjects?**

Pharmacokinetics and pharmacodynamics of insulin glulisine, regular human insulin and insulin lispro in healthy subjects with normal body weight and obese, non-diabetic, healthy subjects following a single subcutaneous dose of 0.3 IU/kg using the euglycemic clamp were studied in two separate studies, Study 1009 and 1010, respectively. The sponsor did not make a cross study comparison between these populations. This reviewer thinks that these set of data will provide additional insight view of insulin resistance from obese population. From the comparison of these two studies with almost identical design, insulin glulisine has exhibited more rapid acting than Lispro in both the initial exposure and response in healthy subjects. However, there is apparently less the initial exposure in obese subjects. Obese subjects also showed that slower time action profiles and less glucodynamic response (Table 10). This pattern is exactly the same as the pattern of difference between type 1 and type 2 diabetic patients. These clamp studies have confirmed the popular observation that obese subjects exhibit less bioavailability of insulin glulisine in the initial time period compared to subjects with normal body weight.

Table 10. Comparison of the initial exposure and response of insulin glulisine in healthy and obsess subjects

Ratio	Healthy subjects (N=16)			Obese non-diabetic subjects (N=8)		
	Glulisine	Lispro	HRI	Glulisine	Lispro	HRI
Pharmacokinetics						
AUC (0-1h)/ AUC(0-clamp end)	27.3%	26.4%	11.5%	16.6%	12.7%	6.5%
AUC (0-2h)/ AUC(0-clamp end)	61.4%	58.5%	32.7%	42.6%	36.5%	21.1%
Pharmacodynamics						
AUC (0-1h)/ AUC(0-clamp end)	11.7%	9.4%	5.4%	6.0%	3.7%	2.0%
AUC (0-2h)/ AUC(0-clamp end)	36.1%	33.2%	20.9%	25.2%	21.8%	13.6%

- **What is the intra-subject variability of pharmacokinetics and pharmacodynamics of insulin glulisine in comparison with insulin lispro and human regular insulin in patients with type 1 diabetes?**

Comparison of intra-subject variability of the pharmacokinetics and pharmacodynamics in type I diabetic patients was performed after administration of 0.2 IU/kg insulin glulisine, insulin lispro and regular human insulin using the euglycemic clamp technique and replicating dosing.

The coefficients of variation within subject (intra-subject) were calculated as average of ratios (AR). The intra-subject variability is summarized in Table 11. The treatment reproducibility of the pharmacokinetic parameters was a little higher for insulin glulisine compared to both insulin lispro and regular human insulin for the initial exposures. However, the intra-subject variability of pharmacodynamics was very similar. Overall intra-subject variability of insulin glulisine is within the ranges for insulin drug products.

Table 11. Intra-subject variability of pharmacokinetics

Variable	Intra-subject CV% (n=16)		
	Glulisine	Lispro	RHI
Pharmacokinetics			
AUC(0-1h) [μIU/min/mL]	19	12	7
AUC(0-2h) [μIU/min/mL]	13	7	7

AUC(0-clamp end) [µIU/min/mL]	5	6	8
Cmax[µIU/mL]			
Tmax [min]	15	18	13
MRT [min]	12	10	12
Pharmacodynamics			
AUC(0-1h) [mg/kg]	29	40	45
AUC(0-2h) [mg/kg]	18	18	22
AUC(0-clamp end) [mg.kg -1]	20	16	22
GIRmax [mg/min.kg]	18	16	18
Tmax [min]	32	24	20

4.3 INTRINSIC FACTORS

4.3.1 Gender

No studies have been designed to explore the topic.

Race:

A comparison of the time-action profiles of insulin glulisine, regular human insulin and insulin lispro was performed after subcutaneous injection of 0.2 IU/kg using the euglycemic clamp technique in healthy male Japanese and Caucasian volunteers in a double-blind, three-way cross-over study. This study demonstrated the more rapid absorption and early action-time profiles of insulin glulisine and insulin lispro in comparison to regular human insulin in young, healthy male Japanese and Caucasian subjects (Table 12).

Table 12. Summary of Pharmacokinetics and Pharmacodynamics in Japanese Subjects

Variable	Geometric mean (N=12)			Geometric mean (N=12)		
	Japanese			Caucasians		
	Glulisine	**Lispro**	**RHI**	**Glulisine**	**Lispro**	**RHI**
Pharmacokinetic						
AUC(0-1h) [µIU.min.mL $^{-1}$]	**5502.0**	4715.3	2088.8	**3553.94**	3672.77	1386.39
AUC(0-2h) [µIU.min.mL $^{-1}$]	**11533.0***	9393.1*	5481.7	**9344.65**	8327.87	4263.69
AUC(0-clamp end) [µIU.min.mL $^{-1}$]	16464.3	14408.9	14805.8	16615.65	14748.49	14374.78
Cmax [µIU/mL]						
Tmax [min]	45.2*	37.4*	78.9	60	43	105
Pharmacodynamics						
AUC(0-1h) [mg.kg $^{-1}$]	226.7	221.0	145.6	145.8	140.0	73.2
AUC(0-2h) [mg.kg $^{-1}$]	677.1	692.3	468.1	449.4	531.9	324.3
AUC(0-clamp end) [mg.kg $^{-1}$]	1767.3	1810.9	2193.2	1307.1	1568.1	1723.1
GIRmax [mg.min $^{-1}$ .kg $^{-1}$]	9.7	10.2	9.8	7.7	8.4	7.9
tmax [min]	134.5	105.5	196.0	161.5	109.5	203.0

*statistically significant difference compared to regular human insulin.

From the table above, there is an apparent trend that the initial exposure-response is greater in Japanese than in Caucasians for all the three insulin products. To further explore the racial difference, the

ratios of early exposure or response to the total exposure or response is calculated and summarized in Table 13.

Table 13. Comparison of time-action profiles between glulisine, lispro and human regular insulin among Japanese and Caucasians

Ratio	Japanese			Caucasians		
	Glulisine	Lispro	RHI	Glulisine	Lispro	RHI
Pharmacokinetic						
AUC(0-1h)/ AUC(0-clamp end)	**0.33**	0.33	0.14	**0.21**	0.25	0.10
AUC(0-2h)/ AUC(0-clamp end)	**0.70**	0.65	0.37	**0.56**	0.56	0.30
Pharmacodynamics						
AUC(0-1h)/ AUC(0-clamp end)	**0.13**	0.12	0.07	**0.11**	0.09	0.04
AUC(0-2h)/ AUC(0-clamp end)	**0.38**	0.38	0.21	**0.34**	0.34	0.19

For the first hour exposure, the AUC ratio is 33% and 21% in Japanese and Caucasians, respectively. Correspondingly, the ratio for the first hour pharmacodynamic response is 13% in Japanese and 11% in Caucasians. Therefore, the Japanese subjects apparently have higher early exposure for all the three insulin products than Caucasians. Because the dosing of insulin is individualized based on the glucose levels, the clinical relevance of minor PK/PD difference in different racial populations may be limited.

Renal impairment:

The impact of renal function on the of pharmacokinetics of insulin glulisine and regular human insulin was studied after subcutaneous injection of 0.15 IU/kg in non-diabetic subjects with different degrees of renal function in a single-dose, 3 center, multinational, open, randomized, 2-way crossover study. Non-diabetic subjects were grouped based on creatinine clearance: Group I: 8 subjects with normal renal function (creatinine clearance >80 mL/min); Group III: 8 subjects with moderate renal impairment (creatinine clearance between 30 to 50 mL/min, inclusive) and Group IV: 8 subjects with severe renal impairment (creatinine clearance <30 mL/min, not requiring hemodialysis). Subjects with minor renal impairment were not proposed for the study, which was supposed to be Group II. Pharmacokinetic results are summarized in Table 14.

Table 14. Pharmacokinetic parameters of insulin glulisine in subjects with renal impairment

Parameter	Geometric mean (CV%)			Ratio		P-value for regression analysis
	Normal	Moderate	Severe	Moderate/ Normal	Severe / Normal	
AUC(0-end) [μIU.min/mL]	13214.5 (31.12)	18472.6 (19.41)	17649.8 (19.29)	1.40	1.34	**0.0030**
AUC(0-2h) [μIU.min/mL]	9005.2 (24.15)	11625.8 (26.08)	9622.0 (17.00)	1.29	1.07	0.3447
AUC(0-1h) [μIU.min/mL]	3946.7 (36.58)	4834.7 (31.01)	3872.2 (20.92)	1.23	0.98	0.9618
Cmax [μIU/mL]	107.8 (29.81)	131.1 (29.23)	107.8 (15.13)	1.22	1.00	0.8131
Tmax [min]	55.9 (29.25)	57.5 (17.60)	67.8 (21.71)	1.03	1.21	0.4502
CLtot/F [mL/min]	852.4 (20.00)	637.3 (20.36)	679.6 (14.01)	0.75	0.80	**0.0048**

The subjects with moderate and severe renal impairment showed the increased exposure of insulin glulisine by 22% to 40% in comparison with normal subjects and the clearance of insulin glulisine was

reduced by 20 –25% in these subjects as well. There were statistically significant correlations for AUC(0-end) and CLtot/F between renal functions as measured by creatinine clearance. Because the impact of moderate renal impairment on insulin glulisine PK appears to have reached a plateau, minor renal impairment may affect the pharmacokinetics of insulin glulisine as well. Unfortunately, this group of subjects was not included in the study.

Hepatic impairment:
No studies have been conducted.

Elderly:
No studies have been conducted.

Pediatric:
The sponsor did not perform any study to compare the difference in pharmacokinetics and pharmacodynamics between adult patients and pediatric patients. However, the sponsor conducted a study to compare the pharmacokinetics and pharmacodynamics for insulin glulisine and human regular insulin in two groups of pediatric patients with type 1 diabetes: 10 prepubertal children (7 to 11 years of age), 10 adolescents (12 to 16 years of age). The study results revealed that insulin glulisine had a rapid acting and shorter residence time compared to regular human insulin. In addition, the pharmacokinetic results showed that adolescents appeared to have a slight trend towards higher exposure than younger children (Table 15).

Figure 4. Average insulin concentration (µIU/mL) after doses of 0.15 IU/kg insulin glulisine (n=20) and regular human insulin (n=19) in pediatric type 1 diabetic patients

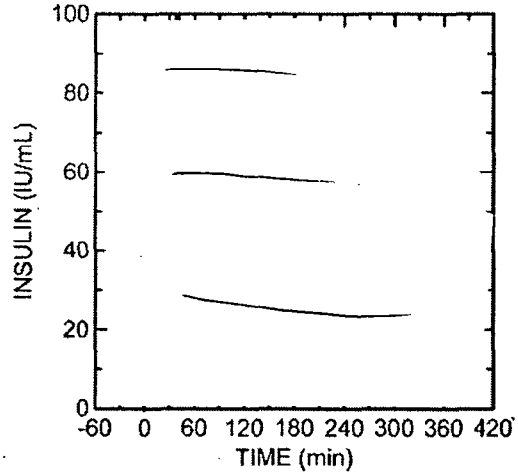


Table 15. Comparison of pharmacokinetic parameters of insulin glulisine in type 1 diabetic adolescents and younger children

Variable	Geometric mean		Point estimate(95% confidence interval) #
	Children(n = 10)	Adolescents(n = 10)	Adolescents / Children(n = 10)
AUC(0-1h) [µIU/min/mL]	2170	2410	111 % (70.4; 175.4 %)
AUC(0-2h) [µIU/min/mL]	4948	5534	112 % (72.0; 173.7 %)
AUC(0-6h) [µIU/min/mL]	7934	8811	111 % (73.0; 169.0 %)
Cmax [µIU /mL]	55	61	112 % (73.0; 171.8 %)
Tmax [min]	55	52	-2 min (-9 ; 11 min)
MRT [min]	87	90	103 % (88.3; 120.9 %)

4.4 Extrinsic Factors

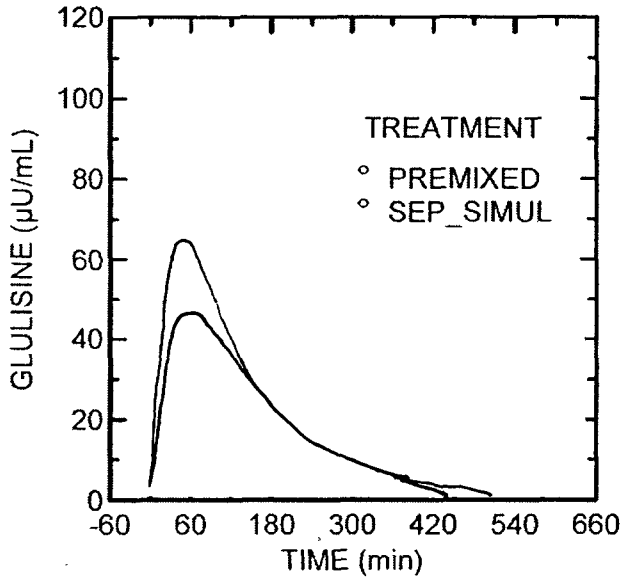
No studies have been conducted to study the effect of insulin glulisine on CYP enzymes.

4.5 General Biopharmaceutics

- **What is the consequence of mixing insulin glulisine with NPH insulin?**

The pharmacokinetic profiles and time action of insulin glulisine of syringe-mixed versus Simultaneous injection of 0.1 IU/kg insulin glulisine and 0.2 IU/kg NPH insulin were studied in 32 male healthy subjects using the euglycemic clamp technique. This was a single-dose, randomized, open-label, two-way, crossover study. Figure 5 depicts the insulin glulisine concentration time profiles: individual profiles (dotted lines) and the fitted average mean profiles (solid line).

Figure 5. Pharmacokinetic profiles of insulin glulisine of simultaneous and premixed with NPH injections



The pharmacokinetic results showed that the total insulin glulisine availability [AUC(0-clamp end)] was about 11% less for immediate premixed with NPH compared to separate simultaneous injections, but 95% confidence interval was very close to bioequivalence criteria. Cmax was attenuated by 27% less and the time to peak exposure (Tmax) was delayed by 3 min when insulin glulisine was immediately premixed with NPH insulin (Table 16).

Table 16. Pharmacokinetic parameters of insulin glulisine after simultaneous injection and premixed

Variable	Geometric mean (arithmetic mean) (N = 32)		Point estimate (95% CI)
	Simultaneous (A)	Premixed (B)	Premixed (B)/ Simultaneous (A)
AUC(0-clamp end) [µIU.min.mL -1]	9261.79 (9401.83)	8251.20 (8843.44)	89.1% (78.1; 101.6%)
Cmax [µIU/mL]	69.98 (71.80)	51.32 (55.39)	73.3% (64.3; 83.6%)
Tmax [min]	47	50	3.9 min (-3.3; 12.4 min)

However, the time to the maximum glucose infusion rate was delayed by 34 min though the total glucose disposal [AUC(0-clamp end)] and maximum glucose infusion rate (GIRmax) were not changed (Table 17). Therefore, premixed regimen did attenuate the rapid acting properties of insulin glulisine. NPH insulin concentrations were not measured in the study. Since this was a euglycemic clamp study, the glucodynamic response would represent a total response from both insulin medications. Although there are

some minor changes in PK and PD parameters, this reviewer agrees with the sponsor that overall these data support mixing of insulin glulisine with NPH insulin in a syringe immediately prior to administration.

Table 17. Pharmacodynamic Parameters of insulin glulisine after simultaneous injection and premixed

Variable	Sample mean (N = 32)		Point estimate/(95% CI)
	Simultaneous (A)	Premixed (B)	Premixed (B)/Simultaneous (A)
$AUC_{(0\text{-clamp end})}$ [mg/kg]	2092.2	2193.2	104.8% (92.2; 119.3%)
GIR_{max} [mg/min.kg]	7.8	7.0	89.9% (80.6; 100.2%)
t_{max} [min]	105	139	29.8 min (0.1; 59.6 min)

4.6 Analytical

- **What is the property of analytical method?**

Insulin glulisine was measured with a specific homologous radioimmunoassay (RIA), which uses the competition between glulisine and [redacted]. The LOQ was [redacted], with a working range of [redacted]. This assay does not cross-react with human insulin, pro-insulin or lispro [redacted] and cross-reacts [redacted] Glulisine was shown to be stable in human serum and plasma under the conditions: (1) room temperature (37°C) for 24 hours [redacted]. The precision and accuracy of the assay are summarized in Table 18.

Table 18. Precision and accuracy of insulin glulisine RIA

	Intra-assay (within-day		Inter-assay (between-day)	
	10 – 150 µIU/mL	Near LOQ	10 – 150 µIU/mL	Near LOQ
Precision (CV)				
Accuracy	[redacted]			

5 LABELING RECOMMENDATIONS

[redacted]

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6 Appendix

6.1 Index for individual studies

Study No.	Title
1001	Pharmacodynamics and pharmacokinetics, safety and tolerance of HMR1153 and HMR1964 in comparison to insulin lispro and regular human insulin in healthy volunteers, using the euglycemic clamp technique
1002	Pharmacodynamics and pharmacokinetics, safety and tolerance of a containing and a -free HMR1964 formulation at two different dosages in healthy volunteers, using the euglycemic clamp technique
1003	Pharmacodynamics and pharmacokinetics, safety and tolerance of a containing HMR1964 formulation, at two different dosages, in comparison to insulin lispro and regular human insulin in healthy volunteers, using the euglycemic clamp technique
1004	Pharmacokinetics, pharmacodynamics and absolute bioavailability of HMR1964 insulin following single intravenous administration and single subcutaneous administration into femoral, deltoid, and abdominal sites in healthy male volunteers, using the euglycemic clamp technique
1005	Comparison of intra-subject variability of the pharmacokinetics and pharmacodynamics in type I diabetic patients after administration of 0.2 IU/kg HMR1964, insulin lispro and regular human insulin using the euglycemic clamp technique and replicate dosing
1006	Pharmacodynamics and pharmacokinetics of HMR1964 (insulin glulisine) compared to insulin lispro and regular human insulin in type 2 diabetic patients using the euglycemic clamp technique
1008	Glucodynamic response to pre- and postmeal subcutaneous injection of 0.15 IU/kg HMR1964 (insulin glulisine) and regular human insulin in type 1 diabetic subjects in an open, randomized, four-way crossover study
1009	Pharmacodynamics and pharmacokinetics, safety and tolerance of the commercial HMR1964 formulation, at two different dosages, in comparison to insulin lispro and regular human insulin in healthy volunteers, using the euglycemic clamp technique
1010	Pharmacokinetics and pharmacodynamics of HMR1964 (insulin glulisine), regular human insulin and insulin lispro in obese, non-diabetic subjects following a single subcutaneous dose of 0.3 IU/kg in a randomized, double blind, three way crossover design, using the euglycemic clamp
1011	Pharmacokinetics of insulin glulisine and regular human insulin after subcutaneous injection of 0.15 IU/kg in non-diabetic subjects with different degrees of renal function in an open, parallel group, two-way crossover, single-dose study
1012	Time action and serum HMR1964 insulin concentration profiles of syringe-mixed versus simultaneously injected 0.1 IU/kg HMR1964 and 0.2 IU/kg NPH insulin in healthy subjects using the euglycemic clamp technique
1013	Comparison of the time-action profiles of HMR1964 (commercial formulation), regular human insulin and insulin lispro after subcutaneous injection of 0.2 IU/kg employing the euglycemic clamp technique in healthy male Japanese and Caucasian volunteers in a double-blind, three-way cross-over study
1016	Comparison of steady state pharmacokinetics and pharmacodynamics at continuous intravenous infusion of 0.8 mIU/kg/min HMR1964 or regular human insulin in healthy volunteers, using a randomized, open label, two-way cross-over design and the euglycemic clamp technique
1017	Pharmacokinetics and safety of 0.15 IU/kg HMR1964 (insulin glulisine) and regular human insulin injected subcutaneously as a single dose in pediatric subjects with type 1 diabetes in a single-center, double-blind, randomized, two-way crossover study

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/s/

Xiao-xiong Wei
3/22/04 02:54:56 PM
BIOPHARMACEUTICS

Hae-Young Ahn
3/22/04 03:48:16 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	**21-629**	**Brand Name**	**Apidra™**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Insulin glulisine (rDNA origin) for injection**
Medical Division	**HFD-510**	**Drug Class**	**protein**
OCPB Reviewer	**Xiaoxiong (Jim) Wei**	**Indication(s)**	**Diabetes, IDDM & NIDDM**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**Solution:** **100 units per mL:** **10 mL vial**
		Dosing Regimen	**Dependent on glucose levels**
Date of Submission	**06/18/2003**	**Route of Administration**	**SC**
Estimated Due Date of OCPB Review	**01/30/2004**	**Sponsor**	**Aventis**
Division Due Date	**02/15/2004**	**Priority Classification**	**S1**
PDUFA Due Date	**04/18/2004**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	[redacted]		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		
multiple dose:	X	3		
Patients-				
single dose:	X			
multiple dose:	X	3		
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X	1		
gender:				

obese	X	1		
pediatrics:	X	1		
geriatrics:				
renal impairment:	X	1		
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	(1)		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
		22		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**YES**	
Comments sent to firm ?		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Briefing In Content:

Aventis has submitted their NDA for insulin glulisine (Apidra™) for the treatment of type 1 and type 2 diabetes. Insulin glulisine is a human insulin analog that is a rapid-acting, parenteral blood glucose lowering agent. Insulin glulisine is produced by recombinant DNA technology and differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid.

Insulin glulisine has a Tmax of 55 min and Cmax of 82 µIU/ml compared to a Tmax of 82 min and Cmax of 46 µIU/ml for regular human insulin after subcutaneous administration of 0.15 IU/kg.

The to-be-marketed formulation has been used in all clinical trials except the studies of 1001, 1992 and 1003.

These 14 completed and fully reported studies are summarized below:

- 10 studies in adult nondiabetic subjects (Studies 1001, 1002, 1003, 1004, 1009, 1010, 1011, 1012, 1013, and 1016);
- 2 studies in adult subjects with type 1 diabetes (Studies 1005 and 1008);
- 1 study in adult subjects with type 2 diabetes (Study 1006).

Foe special populations, the sponsor submitted renal, pediatric, obese and ethnicity (Japanese/White) studies. The sponsor did not submit studies regarding hepatic impairment, protein binding, metabolism, gender.

A total o. studies of analytical methodology development including validation data are submitted.

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/s/

Xiao-xiong Wei
8/4/03 11:37:43 AM
BIOPHARMACEUTICS

Hae-Young Ahn
8/6/03 03:17:34 PM
BIOPHARMACEUTICS